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A Study of Physiological Mechanisms and Inter-Relations  
between Systemic and Regional Blood Volume, Blood  
Flow and Electrolyte Balance

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- 1 -

(1) Renal Hemodynamics, Sodium Excretion, and Extracellular Volume

Laboratory studies investigating the role of hemodynamics in the regulation of sodium excretion and extracellular volume have been continued. Previous progress reports described studies in the dog which demonstrated that renal vascular resistance and/or renal blood flow may influence the renal tubular reabsorption of sodium independently of aldosterone, and that these hemodynamic factors may play a role in the normal physiologic regulation of sodium balance. Additional studies recently concluded [REDACTED] have demonstrated that it is not renal blood flow per se but probably a transmission of perfusion pressure through the renal circulation which is important in determining sodium reabsorption.

Two additional lines of laboratory investigation are dealing with 1) the role of renal hemodynamics in limiting sodium excretion in animals with sodium retention (thoracic inferior vena caval constriction, large aortic-caval fistula), and 2) the mechanisms whereby these hemodynamic factors alter the tubular reabsorption of sodium.

(2) The Effect of Atrial Fibrillation upon the Excretion of a Sodium Load with Observations on the Effect of Cardioversion.

Investigations of the potential role of atrial size and function in regulation of sodium excretion have been continued.

Studies described in previous reports indicated that in patients with mitral stenosis and atrial fibrillation, excretion of a sodium load may

- 2 -

be delayed and incomplete. In these patients, conversion to normal sinus rhythm by electrical countershock consistently and significantly increased the rate and completeness of excretion of the sodium load. Inasmuch as the operative repair of mitral stenosis also improved sodium excretion, it was concluded that obstruction at the mitral valve and atrial fibrillation are factors effecting sodium retention. In order to determine whether these factors are dependent or independent, a series of comparable studies has been begun in patients with arteriosclerotic heart disease and atrial fibrillation, primary myocardial disease and atrial fibrillation, and idiopathic atrial fibrillation. So far, in this group of patients, cardioversion has also tended to improve sodium excretion.

In order to study the pathogenesis of sodium retention associated with mitral stenosis on the one hand and atrial fibrillation on the other, preliminary experiments are being carried out with experimental mitral stenosis and experimental atrial fibrillation in dogs.

(3) The Effect of Abnormal Circulatory States upon the Circulatory Response to Upright Tilt.

The cardiovascular responses of 37 patients with heart disease to prolonged passive upright tilt were studied on 46 occasions and compared to the responses of 10 normal subjects.

Patients with heart disease tolerated the tilt remarkably well. Twenty-four patients with heart disease showed an abnormal response to upright tilt, consisting of a smaller than normal increase in heart rate

- 3 -

and diastolic blood pressure and of less narrowing of the pulse pressure. This response was termed "heart failure response" and was most consistently seen in patients with primary myocardial disease, but occurred in hypertensive heart disease and in all types of valvular disease studied. It did not correlate with cardiac rhythm, degree of clinical heart failure or digitalis status.

It is postulated that increased blood volume, increased vasomotor tone, and adaptation to low cardiac output may play a role in the pathogenesis of increased orthostatic tolerance seen in patients with heart disease.

Many of the patients studied in this manner had undergone full cardiac catheterization and hemodynamic study in the same clinical state.

Analysis of the tilt responses in relation to clinical and hemodynamic measurements, now in progress, may elucidate the mechanism of this response more fully. Potentially, the response to tilt may be useful in evaluating the degree of circulatory congestion or blood volume depletion, and in the evaluation of the effect of therapeutic measures. Study of the pathogenesis of the increased orthostatic tolerance seen in congestive heart failure may add to our understanding, management and prevention of the deconditioning effect of space flight.

Studies of the effects of acute blood volume depletion or repletion upon ~~orthostatic~~ orthostatic tolerance are being continued.

- 4 -

(4) Hemodynamic Effects of Ethacrynic Acid in Normal Subjects and in Patients with Congestive Heart Failure.

As part of an inquiry into the effects of acute changes in plasma volume upon systemic hemodynamics, the potent new diuretic ethacrynic acid was given intravenously to three normal subjects on four occasions, and to five patients with advanced congestive heart failure.

In normal subjects, diuresis averaged 986 ml. in one and one-half hours, accompanied by decreases of 16 and 14 per cent in plasma and blood volumes respectively. While central venous pressure remained unchanged or decreased, stroke index and stroke work index fell in three of four cases, by 31 and 24 per cent respectively. Total peripheral resistance increased in all subjects. Arterio-venous oxygen difference increased consistently, by a mean of 1.12 volume per cent.

In patients with heart failure, diuresis was greater and more prolonged, averaging 1,813 ml. in one and one-half hours. Again, plasma and blood volumes decreased, by 13 and 11 per cent respectively. The elevated central venous pressure fell consistently, from a mean of 16 to 9 mm. Hg., stroke index rose in three and remained unchanged in two, and stroke work index remained unchanged in one and increased in four, from a mean of 24.5 to 29.7 gm. M/beat/M<sup>2</sup>. Cardiac index rose in all patients, from a mean of 1.76 to 2.10 L/min/M<sup>2</sup>. Arterio-venous oxygen difference decreased consistently, from 8.32 to 7.31 volumes per cent. Total peripheral resistance decreased uniformly, by a mean of 17 per cent.

- 5 -

The hemodynamic effects of ethacrynic acid in normal subjects were those of acute volume depletion, whereas in patients with congestive heart failure they were the equivalent of a positive inotropic effect, which in turn potentiated the diuresis.

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